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WO 2004/054987 A1

(54) Title: CATHEPSIN CYSTEINE PROTEASE INHIBITORS AND THEIR USE

(57) Abstract: The present invention relates to compounds and compositions for treating diseases associated with cysteine protease activity. The compounds are reversible inhibitors of cysteine proteases S, K, F, L and B. Of particular interest are diseases associated with Cathepsin S. In addition this invention also discloses processes for the preparation of such inhibitors.

Cathepsin cysteine protease inhibitors and their use.

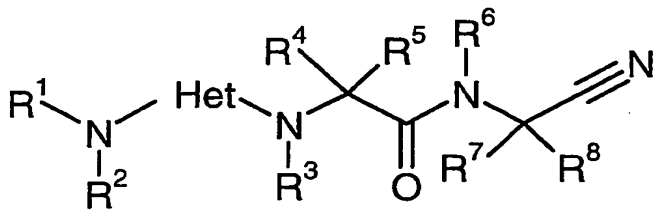
The present invention relates to compounds and compositions for treating diseases associated with cysteine protease activity. The compounds are reversible inhibitors of cysteine proteases S, K, F, L and B. Of particular interest are diseases associated with Cathepsin S. In addition this invention also discloses processes for the preparation of such inhibitors.

BACKGROUND OF THE INVENTION

Cathepsin S is a member of the papain superfamily of cysteine proteases which also encompasses Cathepsins B, H, L, O and K. Cathepsin S plays a key role in the processing of invariant chain in MHC class II complexes allowing the complex to associate with antigenic peptides. MHC class II complexes are then transported to the surface of the cell for presentation to effector cells such as T cells. The process of antigen presentation is a fundamental step in initiation of the immune response. In this respect inhibitors of cathepsin S could be useful agents in the treatment of inflammation and immune disorders such as, but not limited to, asthma, rheumatoid arthritis, multiple sclerosis and Crohn's disease. Cathepsin S has also been implicated in a variety of other diseases involving extracellular proteolysis such as the development of emphysema in COPD through degradation of elastin and in Alzheimers disease.

Other Cathepsins notably K and L have been shown to degrade bone collagen and other bone matrix proteins. Inhibitors of these cysteine proteases would be expected to be useful in the treatment of diseases involving bone resorption such as osteoporosis.

The present invention therefore provides a compound of formula (I)



(I)

R^1 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl

R^2 is independently aryl, heteroaryl or a group C_{1-6}alkylR^9, $CO(C_{1-6}alkyl)R^9$ or $SO_2(C_{1-6}alkyl)R^9$; where R^9 is aryl or heteroaryl

or R^1 and R^2 together with the nitrogen atom to which they are attached form a 4 to 7-membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by one or more C_{1-6} alkyl, amino, hydroxy, CO_2C_{1-6} alkyl, COC_{1-6} alkyl, halogen, C_{1-6} alkylhydroxy, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR^1 group, C_{1-6} alkyl$NR^{12}R^{13}$ where R^{12} and R^{13} are independently hydrogen or C_{1-6} alkyl, $CONR^{12}R^{13}$, or optionally substituted by C_{1-6}alkylR^9, aryl, phenoxy, COaryl, COheteroaryl or a heteroaryl group, the latter six groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, $CONR^{12}R^{13}$, $SO_2NR^{12}R^{13}$, SO_2R^{12}, trifluoromethyl, $NHSO_2R^{12}$, $NHCOR^{12}$, ethylenedioxy, methylenedioxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl $NR^{10}R^{11}$, SR^{12} or $NR^{10}R^{11}$;

Het is a heteroaryl ring chosen from pyridine, pyrimidine, pyrazine, pyridazine or triazine and optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, $CONR^{12}R^{13}$, $SO_2NR^{12}R^{13}$, SO_2R^{12}, trifluoromethyl, $NHSO_2R^{12}$, $NHCOR^{12}$, C_{1-6} alkyl, C_{1-6} alkoxy, SR^{12} or $NR^{10}R^{11}$;

R^3 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^4 is independently hydrogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, arylC_{1-5}alkyl or heteroarylC_{1-5}alkyl, the latter three groups being optionally substituted by one or more halogen, amino, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, SR^{12} or $NR^{10}R^{11}$;

R^5 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^6 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^7 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^8 is independently hydrogen, aryl, heteroaryl or C_{1-6} alkyl optionally substituted with one or more aryl, heteroaryl, halogen, amino, hydroxy, carboxy, $CONR^{12}R^{13}$, $SO_2NR^{12}R^{13}$, SO_2R^{12}, $NHSO_2R^{12}$, $NHCOR^{12}$, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, SR^{12} or $NR^{10}R^{11}$;

or a pharmaceutically acceptable salt thereof.

Aryl groups include phenyl and naphthyl. Heteroaryl groups include 5- or 6- membered, 5,6- or 6,6-fused heterocyclic rings containing one or more heteroatoms selected from N, S or O. Examples include pyridinyl, pyrimidinyl, thiazolyl, oxazolyl, pyrazole, imidazolyl, furyl, thienyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzofuryl, benzothienyl and indolyl.

Aryl and heteroaryl groups can be optionally substituted by on or more of the following groups; halogen, amino, hydroxy, cyano, nitro, carboxy, $CONR^{12}R^{13}$, $SO_2NR^{12}R^{13}$, SO_2R^{12}, trifluoromethyl, $NHSO_2R^{12}$, $NHCOR^{12}$, ethylenedioxy, methylenedioxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl $NR^{10}R^{11}$, SR^{12} or $NR^{10}R^{11}$.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

Preferably R^1 is hydrogen or C_{1-6}alkyl, more preferably methyl and R^2 is CH_2R^9 or $CH_2CH_2R^9$ where R^9 is phenyl or a 5- or 6-membered aromatic ring containing one or two heteroatoms and optionally substituted by C_{1-6}alkyl. More preferably R^2 is CH_2R^9 or $CH_2CH_2R^9$ where R^9 is phenyl, pyridyl or oxazole substituted by methyl.

Alternatively R^1 and R^2 form a piperidine, piperazine, pyrrolidine, morpholine, or thiomorpholine ring optionally substituted by CH_2OH, CH_2CH_2OH, hydroxy, $CONH_2$, phenyl, phenoxy, C(O)-furyl, the latter three groups being optionally substituted by halogen, in particular chloro.

Preferably Het is pyrimidine ring.

Preferably R^3 is hydrogen.

Preferably R^4 is hydrogen.

Preferably R^5 is C_{1-6} alkyl, more preferably iso-butyl.

Preferably R^6 is hydrogen.

Preferably R^7 and R^8 are both hydrogen.

Preferred compounds of the invention include:

N~1~-[Cyano(2-methoxyphenyl)methyl]-N~2~-(2-morpholin-4-ylpyrimidin-4-yl)-L-leucinamide

N~1~-[Cyano(2-methoxyphenyl)methyl]-N~2~-(2-piperazin-1-ylpyrimidin-4-yl)-L-leucinamide,

N-[Cyano(2-methoxyphenyl)methyl]-N-(2-morpholin-4-ylpyrimidin-4-yl)-L-phenylalaninamide

N~1~-[Cyano(2-methoxyphenyl)methyl]-3-cyclohexyl-N~2~-(2-morpholin-4-ylpyrimidin-4-yl)-L-alaninamide

N-[2-(Benzylamino)pyrimidin-4-yl]-N-(cyanomethyl)-L-phenylalaninamide

N-{2-[Benzyl(methyl)amino]pyrimidin-4-yl}-N-(cyanomethyl)-L-phenylalaninamide

N-{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N-(cyanomethyl)-L-phenylalaninamide

N~2~-[2-(Benzylamino)pyrimidin-4-yl]-N~1~-(cyanomethyl)-3-cyclohexyl-L-alaninamide

N~2~-{2-[Benzyl(methyl)amino]pyrimidin-4-yl}-N~1~-(cyanomethyl)-3-cyclohexyl-L-alaninamide

N~2~-{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-3-cyclohexyl-L-alaninamide

N~1~-(Cyanomethyl)-N~2~-(4-morpholin-4-ylpyrimidin-2-yl)-L-leucinamide

N~1~-(Cyanomethyl)-N~2~-(2-morpholin-4-ylpyrimidin-4-yl)-L-leucinamide

N~1~-(Cyanomethyl)-N~2~-[2-(4-hydroxy-4-phenylpiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide

N~1~-(Cyanomethyl)-N~2~-{2-[methyl(pyridin-3-ylmethyl)amino]pyrimidin-4-yl}-L-leucinamide

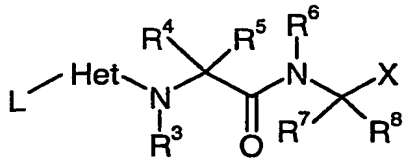
N~2~-{2-[Benzyl(methyl)amino]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide

N~2~-{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide,
N~2~-{2-[4-(5-Chloropyridin-2-yl)piperazin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide,
N~1~-(Cyanomethyl)-N~2~-{2-[methyl(thien-3-ylmethyl)amino]pyrimidin-4-yl}-L-leucinamide
N~1~-(Cyanomethyl)-N~2~-(2-thiomorpholin-4-ylpyrimidin-4-yl)-L-leucinamide
N~1~-(Cyanomethyl)-N~2~-[2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl]-L-leucinamide
N~1~-(Cyanomethyl)-N~2~-{2-[2-(hydroxymethyl)piperidin-1-yl]pyrimidin-4-yl}-L-leucinamide
N~1~-(Cyanomethyl)-N~2~-{2-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]pyrimidin-4-yl}-L-leucinamide
N~1~-(Cyanomethyl)-N~2~-[2-(4-hydroxypiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide
N~1~-(Cyanomethyl)-N~2~-{2-[4-(2-furoyl)piperazin-1-yl]pyrimidin-4-yl}-L-
N~2~-{2-[3-(Aminocarbonyl)piperidin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide
N~1~-(Cyanomethyl)-N~2~-{2-[methyl(2-pyridin-2-ylethyl)amino]pyrimidin-4-yl}-L-leucinamide
N~2~-[2-(4-Benzylpiperidin-1-yl)pyrimidin-4-yl]-N~1~-(cyanomethyl)-L-leucinamide
N~1~-(Cyanomethyl)-N~2~-[2-(4-pyridin-2-ylpiperazin-1-yl)pyrimidin-4-yl]-L-leucinamide
N~1~-(Cyanomethyl)-N~2~-[2-(4-phenylpiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide
N~1~-(Cyanomethyl)-N~2~-{2-[4-(2-hydroxyethyl)piperidin-1-yl]pyrimidin-4-yl}-L-leucinamide
N~2~-{2-[4-(3-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide
N~1~-(Cyanomethyl)-N~2~-[2-(4-phenoxypiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide
N~1~-(Cyanomethyl)-N~2~-[2-(3-phenylpyrrolidin-1-yl)pyrimidin-4-yl]-L-leucinamide
N~1~-(Cyanomethyl)-N~2~-(2-{methyl[(3-methylisoxazol-5-yl)methyl]amino}pyrimidin-4-yl)-L-leucinamide

and pharmaceutically acceptable salts thereof.

The present invention further provides a process for the preparation of a compound of formula (I) which comprises

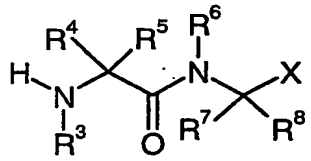
(i) reaction of a compound of general formula (II)



(II)

wherein L represents a leaving group (e.g. halide, sulphide, sulfoxide or sulphone group), preferably the sulphide is oxidised to a sulphoxide or sulphone group before displacement. An oxidising agent such as a peracid may be used, for example meta-chloroperbenzoic acid in dichloromethane at room temperature.
L may be displaced by NR^1R^2 respectively where R^1 and R^2 are defined in formula (I). The reaction may be performed in an inert solvent for example dioxane, N,N-dimethylformamide at ambient temperature or with heating, usually with a base present for example N,N-diisopropylethylamine.

X may be CN, or a group that can be readily converted into a nitrile, for example C1-6alkoxycarbonyl, $CONH_2$ or CO_2H.

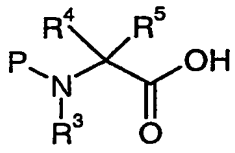


(III)

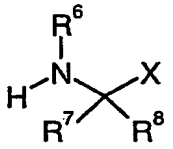
(IV)

Compounds of formula (II) may be prepared from compounds of formula (III) by displacement of a leaving group L^1 from compounds of formula (IV).
Wherein L^1 represents a leaving group (e.g. halide, sulphide, sulfoxide or sulphone group), preferably the sulphide is oxidised to a sulphoxide or sulphone group before displacement. An oxidising agent such as a peracid may be used, for example meta-chloroperbenzoic acid in dichloromethane at room temperature. The reaction may be performed in an inert solvent for example dioxane, N,N-dimethylformamide at ambient temperature or with heating, usually with a base present for example N,N-diisopropylethylamine.

Compounds of formula (III) may be prepared from the reaction of compounds of formula (V) with compounds of formula (VI) using an appropriate coupling agent , for example N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide, carbonyl diimidazole. Alternatively the acid may be activated by formation of the acid chloride using for example, oxalyl chloride.



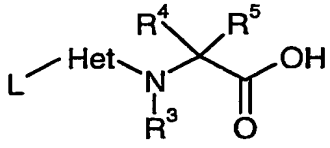
(V)



(VI)

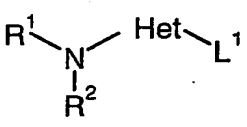
P is a nitrogen protecting group for example tert-butylcarbamate, benzyl carbamate, benzyl.

Compound of general formula (II) may also be prepared from the reaction of compounds of formula (VII) with compounds of formula (VI) using an appropriate coupling agent , for example N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide, carbonyl diimidazole. Alternatively the acid may be activated by formation of the acid chloride using for example, oxalyl chloride.

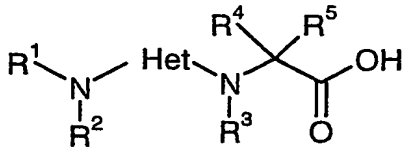


(VII)

(ii) reaction of a compound of general formula (VIII) with compounds of formula (III) or reaction of a compound of general formula (IX) with a compound of general formula (VI).



(VIII)



(IX)

According to a further feature of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt thereof, for use as a therapeutic agent.

According to a further feature of the present invention there is provided a method for producing inhibition of a cysteine protease in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof. In particular the compounds of the invention are useful in the treatment of inflammation and immune disorders such as, but not limited to, asthma, rheumatoid arthritis, COPD, multiple sclerosis, Crohn's disease, Alzheimers and pain, such as neuropathic pain. Preferably the compounds of the invention are used to treat pain, especially neuropathic pain.

The invention also provides a compound of the formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament; and the use of a compound of the formula (I) of the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of a cysteine protease in a warm blooded animal, such as man.

In particular the invention provides the use of a compound of the formula (I) of the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of Cathepsin S in a warm blooded animal, such as man. In order to use a compound of the formula (I) or a pharmaceutically acceptable salt thereof for the therapeutic treatment of mammals including humans, in particular in the inhibition of a cysteine protease, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders,

suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 100 mg and 1 g of the compound of this invention.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 1 $mgkg^{-1}$ to 100 $mgkg^{-1}$ of the compound, preferably in the range of 5 $mgkg^{-1}$ to 20 $mgkg^{-1}$ of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically-acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg/tablet
Compound X.	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β cyclodextrin may be used to aid formulation.

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

The following examples illustrate the invention.

Example 1

N~1~--[Cyano(2-methoxyphenyl)methyl]-N~2~--(2-morpholin-4-ylpyrimidin-4-yl)-L-leucinamide

(i) N~2~--(tert-Butoxycarbonyl)-N~1~--[cyano(2-methoxyphenyl)methyl]-L-leucinamide

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.9g) and 1-hydroxybenzotriazole hydrate (2.0g) were added to a solution of 2-methoxyphenylamino acetonitrile (2.0g) and N-tert-butoxycarbonyl L-leucine (2.5g) in N,N-dimethylformamide (20ml) at room temperature followed by N,N-diisopropylethylamine (5.3ml) and stirred at room temperature overnight. The mixture was diluted with water, extracted into ethyl acetate and dried($MgSO_4$). The solvent was removed under vacuum to leave an oil which was subjected to column chromatography on silica eluting with isohexane/ethyl acetate 2:1 to give a colourless oil (3.7g).

MS: APCI(+ve) 249(M-Boc-CN+1)

(ii) N~1~--[Cyano(2-methoxyphenyl)methyl]-L-leucinamide

The product from step (i) (3.70g) in formic acid (40ml) was stirred for 90min at room temperature then the solvent was removed under vacuum to give a yellow oil (2.7g).

MS: APCI(+ve) 276(M-Boc+1)

(iii) N~1~--[Cyano(2-methoxyphenyl)methyl]-N~2~--(2-fluoropyrimidin-4-yl)-L-leucinamide

A solution of the product from step (ii) (2.7g) and N,N-diisopropylethylamine (1.7ml) in tetrahydrofuran (40ml) was added dropwise to a solution of 2,4-difluoropyrimidine (1.15g) in tetrahydrofuran (40ml) and N,N-diisopropylethylamine (1.7ml). After stirring at room temperature overnight the solvent was removed under vacuum to yield a crude oil which was subjected to column chromatography on silica eluting with dichloromethane/ethyl acetate 2:1 to give a colourless oil (1.50g).

MS: APCI(+ve) 372(M+1)

(iv) N~1~--[Cyano(2-methoxyphenyl)methyl]-N~2~--(2-morpholin-4-ylpyrimidin-4-yl)-L-leucinamide

The product from step (iii) (0.5g), morpholine (0.12ml) and N,N-diisopropylethylamine (0.24ml) in tetrahydrofuran (20ml) was stirred at room temperature overnight. The solvent was removed under vacuum to yield a crude oil which was subjected to column chromatography on silica eluting with ethyl acetate/isohexane 3:1 to give a white solid (0.4g).

MS: APCI(+ve) 439(M+1)
1H NMR: δ (DMSO) 9.40 (1H, m), 9.08 (1H, m), 7.78-7.12 (5H, m), 6.10-6.08 (1H, d), 5.80 (1H, m), 4.60-4.40 (1H, m), 3.84-3.51 (11H, m), 1.80-1.20(3H, m), 0.96-0.84 (6H, m).

Example 2
N~1~-[Cyano(2-methoxyphenyl)methyl]-N~2~-(2-piperazin-1-ylpyrimidin-4-yl)-L-leucinamide, trifluoroacetate salt

The title compound was prepared according to the procedure in example 1 step (iv) using piperazine.

MS: APCI(+ve) 438(M+1)
1H NMR: δ (DMSO) 8.83-8.81 (2H, m), 7.79-6.97 (5H, m), 6.09-6.02 (2H, m), 4.40 (1H, m), 3.85 (7H, bm), 3.13-3.05 (4H, m), 1.68-1.49 (3H, m), 0.94-0.84 (6H, m).

Example 3
N-[Cyano(2-methoxyphenyl)methyl]-N-(2-morpholin-4-ylpyrimidin-4-yl)-L-phenylalaninamide

(i) N-(tert-Butoxycarbonyl)-N-[cyano(2-methoxyphenyl)methyl]-L-phenylalaninamide
The sub-title compound was prepared from N-butoxycarbonyl-L-phenylalanine (1.32g) by the method of example 1 step (i). Yield 2.05g.

MS: APCI(+ve) 310 (M-Boc+1)

(ii) N-[Cyano(2-methoxyphenyl)methyl]-N-(2-fluoropyrimidin-4-yl)-L-phenylalaninamide

The sub-title compound was prepared from the product of step (i) (2.05g) by the method of example 1 steps (ii) and (iii). Yield 0.57g.

MS: APCI(+ve) 406 (M+1)

(iii) N-[Cyano(2-methoxyphenyl)methyl]-N-(2-morpholin-4-ylpyrimidin-4-yl)-L-phenylalaninamide

The title compound was prepared from the product of step (ii)(0.25g) by the method of example 1 step (iv). Yield 0.078g.

MS: APCI(+ve) 473 (M+1)
NMR: δ (DMSO) 9.29 and 9.15 (1H, 2xd), 7.73 and 7.69 (1H, 2xd), 7.45-7.40 (2H,m), 7.33-7.17 (6H,m), 7.11 (1H,m), 7.00 (1H,m), 6.08 (1H,dd), 5.88 and 5.85 (1H,2xd), 4.64 (1H, brs), 3.83 and 3.80 (3H, 2xs), 3.58 (4H,m), 3.47 (4H,m), 3.05-2.82 (2H,m).

Example 4
N~1~-[Cyano(2-methoxyphenyl)methyl]-3-cyclohexyl-N~2~-(2-morpholin-4-ylpyrimidin-4-yl)-L-alaninamide

(i) N-(tert-Butoxycarbonyl)-N-[cyano(2-methoxyphenyl)methyl]-3-cyclohexyl-L-alaninamide
The sub-title compound was prepared from N-butoxycarbonyl-beta-cyclohexyl-L-alanine (1.36g) by the method of example 1 step (i). Yield 1.99g. Used directly in the next step.

(ii) N~1~-[Cyano(2-methoxyphenyl)methyl]-3-cyclohexyl-N~2~-(2-fluoropyrimidin-4-yl)-L-alaninamide
The sub-title compound was prepared from the product of step (i) (1.99g) by the method of example 1 steps (ii) and (iii). Yield 0.12g.

MS: APCI(+ve) 412 (M+1)

(iii) N~1~-[Cyano(2-methoxyphenyl)methyl]-3-cyclohexyl-N~2~-(2-morpholin-4-ylpyrimidin-4-yl)-L-alaninamide

The title compound was prepared from the product of step (ii) (0.12g) by the method of example 1 step (iv). Yield 0.087g.

MS: APCI(+ve) 479 (M+1)
NMR: δ (DMSO) 9.18 and 9.06 (1H,2xd), 7.76 and 7.72 (1H,2xd), 7.49-7.37 (2H,m), 7.24 (1H,brs), 7.11 (1H,d), 7.02 (1H,t), 6.09 (1H,m), 5.91 and 5.88 (1H,2xd), 4.46 and 4.36 (1H,2xbrs,), 3.82 and 3.80 (3H,2xs), 3.60 (4H,m), 3.47 (4H,m), 1.76-1.36 (8H,m), 1.24-1.09 (3H,m), 0.98-0.83 (2H,m).

Example 5
N-[2-(Benzylamino)pyrimidin-4-yl]-N-(cyanomethyl)-L-phenylalaninamide

(i) N-(tert-Butoxycarbonyl)-N-(cyanomethyl)-L-phenylalaninamide
The sub-title compound was prepared from aminoacetonitrile hydrochloride by the method of example 1 step (i).

MS: APCI(+ve) 204 (M-Boc+1)

(ii) N-(Cyanomethyl)-N-(2-fluoropyrimidin-4-yl)-L-phenylalaninamide
The sub-title compound was prepared from the product of step (i) (3.5g) by the method of example 1 steps (ii) and (iii). Yield 1.11g.

MS: APCI(+ve) 300 (M+1)

(iii) N-[2-(Benzylamino)pyrimidin-4-yl]-N-(cyanomethyl)-L-phenylalaninamide
The title compound was prepared from the product from step (ii) (0.2g) and benzylamine (0.37ml) by the method of example 1 step (iv). Yield 0.11g.

MS: APCI(+ve) 387 (M+1)
NMR: δ (DMSO) 8.60 (1H,brs), 7.61 (1H,d), 7.29-7.14 (10H,m), 6.93 (1H,brs), 5.78 (1H,d), 4.64 (1H,brs), 4.47-4.33 (2H,m), 4.05 (2H,brs), 3.03 (1H,dd), 2.85 (1H,m).

Example 6
N-{2-[Benzyl(methyl)amino]pyrimidin-4-yl}-N-(cyanomethyl)-L-phenylalaninamide

The title compound was prepared from the product of example 5 step (ii) (0.2g) and N-benzylmethylamine by the method of example 1 step (iv). Yield 0.18g.

MS: APCI(+ve) 401 (M+1)
NMR: δ (DMSO) 8.69 (1H,brs), 7.71 (1H,d), 7.33-7.15 (10H,m), 5.84 (1H,d), 4.75 (2H,q), 4.62 (1H,brs), 4.03 (2H,brs), 2.99 (1H,dd), 2.94 (3H,s), 2.86 (1H,m).

Example 7
N-{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N-(cyanomethyl)-L-phenylalaninamide

The title compound was prepared from the product of example 5 step (ii) (0.2g) and 4(4-chlorophenyl)piperazine by the method of example 1 step (iv). Yield 0.18g.

MS: APCI(+ve) 476 (M+1)
NMR: δ (DMSO) 8.77 (1H,t), 7.72 (1H,d), 7.40 (1H,brs), 7.31-7.17 (7H,m), 6.98 (2H,d), 5.86 (1H,d), 4.54 (1H,brs), 4.13 (2H,m), 3.74 (4H,m), 3.12 (4H,m), 3.01 (1H,dd), 2.89 (1H,m).

Example 8
N~2~-[2-(Benzylamino)pyrimidin-4-yl]-N~1~-(cyanomethyl)-3-cyclohexyl-L-alaninamide

(i) N-(tert-butoxycarbonyl)-N-(cyanomethyl)-3-cyclohexyl-L-alaninamide
The sub-title compound was prepared from N-butoxycarbonyl-beta-cyclohexyl-L-alanine (5.0g) and aminoacetonitrile hydrochloride (1.71g) by the method of example 1 step (i). Yield 4.09g.

MS: APCI(+ve) 210 (M-Boc+H)

(ii) N~1~-(Cyanomethyl)-3-cyclohexyl-N~2~-(2-fluoropyrimidin-4-yl)-L-alaninamide
The sub-title compound was prepared from the product of step (i) (4.09g) by the method of example 1 steps (ii) and (iii). Yield 1.00g.

MS: APCI(+ve) 306 (M+1)

(iii) N~2~-[2-(Benzylamino)pyrimidin-4-yl]-N~1~-(cyanomethyl)-3-cyclohexyl-L-alaninamide

The title compound was prepared from the product of step (ii) (0.2g) by the method of example 1 step (iv). Yield 0.05g.

MS: APCI(+ve) 393 (M+1)
NMR: δ (DMSO) 8.48 (1H,brs), 7.64 (1H,d), 7.31-7.24 (4H,m), 7.17 (1H,m), 7.09 (1H,brs), 6.93 (1H,brs), 5.81 (1H,d), 4.47-4.36 (3H,m), 4.04 (2H,d), 1.75-1.47 (7H,m), 1.31 (1H,m), 1.19-1.09 (3H,m), 0.86 (2H,m).

Example 9

N~2~-{2-[Benzyl(methyl)amino]pyrimidin-4-yl}-N~1~-(cyanomethyl)-3-cyclohexyl-L-alaninamide

The title compound was prepared from the product of example 8 step (ii) (0.2g) and N-benzylmethylamine (0.43ml) by the method of example 1 step (iv). Yield 0.13g.

MS: APCI(+ve) 407 (M+1)
NMR: δ (DMSO) 8.57 (1H,brs), 7.73 (1H,d), 7.31-7.27 (2H,m), 7.23-7.19 (4H,m), 5.85 (1H,d), 4.80 (2H,m), 4.42 (1H,brs), 4.02 (2H,m), 2.95 (3H,s), 1.69-1.44 (7H,m), 1.35 (1H,m), 1.24-1.07 (3H,m), 0.92-0.81 (2H,m).

Example 10

N~2~-{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-3-cyclohexyl-L-alaninamide

The title compound was prepared from the product of example 8 step (ii) (0.2g) and 4(4-chlorophenyl)piperazine (0.66g) by the method of example 1 step (iv). Yield 0.2g.

MS: APCI(+ve) 482 (M+1)
NMR: δ (DMSO) 8.66 (1H,t), 7.75 (1H,d), 7.25 (3H,d), 6.98 (2H,d), 5.89 (1H,d), 4.35 (1H,brs), 4.12 (2H,d), 3.75 (4H,m), 3.13 (4H,m), 1.73-1.46 (7H,m), 1.37 (1H,m), 1.24-1.07 (3H,m), 0.97-0.87 (2H,m).

Example 11

N~1~~-(Cyanomethyl)-N~2~~-(4-morpholin-4-ylpyrimidin-2-yl)-L-leucinamide

(i) N~2~~-(tert-Butoxycarbonyl)-N~1~~-(cyanomethyl)-L-leucinamide

The sub-title compound was prepared according to the procedure of example 1 step (i) with amino acetonitrile hydrochloride (2.22g) and N-tert-butoxy S-leucine (5g).

MS: APCI(+ve) 270(M+1)

(ii) N~1~~-(Cyanomethyl)-N~2~~-(4-fluoropyrimidin-2-yl)-L-leucinamide and N~1~~-(Cyanomethyl)-N~2~~-(2-fluoropyrimidin-4-yl)-L-leucinamide

The sub-title compounds were prepared from the product of step (i) (4.3g) according to the procedure of example 1 steps (ii) and (iii).

N~1~~-(Cyanomethyl)-N~2~~-(4-fluoropyrimidin-2-yl)-L-leucinamide
Yield 0.38g
MS: APCI(+ve) 266(M+1)

N~1~~-(Cyanomethyl)-N~2~~-(2-fluoropyrimidin-4-yl)-L-leucinamide
Yield 3.8g
MS: APCI(+ve) 266(M+1)

(iii) N~1~~-(Cyanomethyl)-N~2~~-(4-morpholin-4-ylpyrimidin-2-yl)-L-leucinamide

The title compound was prepared according to the procedure of example 1 step (iv) using N~1~~-(cyanomethyl)-N~2~~-(4-fluoropyrimidin-2-yl)-L-leucinamide. Yield 0.2g

MS: APCI(+ve) 333(M+1)
1H NMR: δ (DMSO) 8.49-8.46 (1H, t), 7.83-7.81 (1H, d), 6.63 (1H, bm), 6.06-6.04 (1H, d), 4.25-4.05 (3H, m), 3.63-3.47 (8H, m), 1.75-1.39 (3H, m), 0.90-0.84 (6H, m).

Example 12

N~1~~-(Cyanomethyl)-N~2~~-(2-morpholin-4-ylpyrimidin-4-yl)-L-leucinamide

The title compound was prepared from N~1~-(cyanomethyl)-N~2~-(2-fluoropyrimidin-4-yl)-L-leucinamide (example 11 step (iii)) according to the procedure of example 1 step (iv). Yield 0.17g

MS: APCI(+ve) 333(M+1)
1H NMR: δ (DMSO) 8.64-8.60 (1H, t), 7.74-7.72 (1H, d), 7.24-7.23 (1H, d), 5.89-5.82 (1H, d), 4.31-4.08 (3H, m), 3.58 (8H, m), 1.72-1.39 (3H, m), 0.92-0.84 (6H, m).

Examples 13-34 were prepared according to the procedures of example 1 step (iv) using N~1~-(cyanomethyl)-N~2~-(2-fluoropyrimidin-4-yl)-L-leucinamide (example 11 step (iii)) and the appropriate amine.

Example 13
N~1~-(Cyanomethyl)-N~2~-[2-(4-hydroxy-4-phenylpiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide

MS: APCI(+ve) 423(M+1)
1H NMR: δ (DMSO) 8.65-8.61 (1H, t), 7.73-7.14 (7H, m), 5.84-5.82 (1H, d), 5.00-4.39 (4H, m), 4.08-4.03 (2H, m), 3.20-3.12 (2H, m), 1.90-1.35 (7H, m), 0.92-0.85 (6H, m).

Example 14
N~1~-(Cyanomethyl)-N~2~-{2-[methyl(pyridin-3-ylmethyl)amino]pyrimidin-4-yl}-L-leucinamide

MS: APCI(+ve) 368(M+1)
1H NMR: δ (DMSO) 8.59-7.20 (7H, m), 5.89-5.87 (1H, d), 4.68 & 4.37 (3H, m), 4.08-4.02 (2H, m), 2.99 (3H, s), 1.68-1.35 (3H, m), 0.93-0.80 (6H, m).

Example 15
N~2~-{2-[Benzyl(methyl)amino]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide

MS: APCI(+ve) 367(M+1)
1H NMR: δ (DMSO) 8.57-8.54 (1H, t), 7.74 (1H, d), 7.31-7.18 (6H, m), 5.87-5.85 (1H, d), 4.82-4.00 (5H, m), 2.95 (3H, s), 1.71-1.40 (3H, m), 0.89-0.81 (6H, m).

Example 16

N~2~~{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N~1~~(cyanomethyl)-L-leucinamide, trifluoroacetate salt

MS: APCI(+ve) 442(M+1)

1H NMR: δ (DMSO) 9.02-9.01 (2H, m), 7.75-6.98 (5H, m), 6.24-6.22 (1H, d), 4.48-4.13 (3H, m), 3.82-3.55 (8H, m), 1.66-1.50 (3H, m), 0.95-0.88 (6H, m).

Example 17

N~2~~{2-[4-(5-Chloropyridin-2-yl)piperazin-1-yl]pyrimidin-4-yl}-N~1~~(cyanomethyl)-L-leucinamide, bis trifluoroacetate salt

MS: APCI(+ve) 443(M+1)

1H NMR: δ (DMSO) 9.03-9.01 (2H, m), 8.15-6.90 (4H, m), 6.25-6.23 (1H, d), 4.49 (1H, m), 4.23-4.18 (2H, d), 3.80-3.66 (8H, m), 1.66-1.51 (3H, m), 0.95-0.88 (6H, m).

Example 18

N~1~~(Cyanomethyl)-N~2~~{2-[methyl(thien-3-ylmethyl)amino]pyrimidin-4-yl}-L-leucinamide

MS: APCI(+ve) 373(M+1)

Example 19

N~1~~(Cyanomethyl)-N~2~~(2-thiomorpholin-4-ylpyrimidin-4-yl)-L-leucinamide

MS: APCI(+ve) 349(M+1)

Example 20

N~1~~(Cyanomethyl)-N~2~~[2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl]-L-leucinamide

MS: APCI(+ve) 408(M+1)

Example 21

N~1~-(Cyanomethyl)-N~2~-{2-[2-(hydroxymethyl)piperidin-1-yl]pyrimidin-4-yl}-L-leucinamide

MS: APCI(+ve) 361(M+1)

Example 22
N~1~-(Cyanomethyl)-N~2~-{2-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]pyrimidin-4-yl}-L-leucinamide

MS: APCI(+ve) 347(M+1)

Example 23
N~1~-(Cyanomethyl)-N~2~-[2-(4-hydroxypiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide

MS: APCI(+ve) 347(M+1)

Example 24
N~1~-(Cyanomethyl)-N~2~-{2-[4-(2-furoyl)piperazin-1-yl]pyrimidin-4-yl}-L-leucinamide

MS: APCI(+ve) 426(M+1)

Example 25
N~2~-{2-[3-(Aminocarbonyl)piperidin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide

MS: APCI(+ve) 374(M+1)

Example 26
N~1~-(Cyanomethyl)-N~2~-{2-[methyl(2-pyridin-2-ylethyl)amino]pyrimidin-4-yl}-L-leucinamide

MS: APCI(+ve) 382(M+1)

Example 27

N~2~-[2-(4-Benzylpiperidin-1-yl)pyrimidin-4-yl]-N~1~-(cyanomethyl)-L-leucinamide

MS: APCI(+ve) 421(M+1)

Example 28
N~1~-(Cyanomethyl)-N~2~-[2-(4-pyridin-2-ylpiperazin-1-yl)pyrimidin-4-yl]-L-leucinamide

MS: APCI(+ve) 409(M+1)

Example 29
N~1~-(Cyanomethyl)-N~2~-[2-(4-phenylpiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide

MS: APCI(+ve) 407(M+1)

Example 30
N~1~-(Cyanomethyl)-N~2~-{2-[4-(2-hydroxyethyl)piperidin-1-yl]pyrimidin-4-yl}-L-leucinamide

MS: APCI(+ve) 375(M+1)

Example 31
N~2~-{2-[4-(3-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide

MS: APCI(+ve) 442/4(M+1)

Example 32
N~1~-(Cyanomethyl)-N~2~-[2-(4-phenoxypiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide

MS: APCI(+ve) 423(M+1)

Example 33

N~1~~-(Cyanomethyl)-N~2~~-[2-(3-phenylpyrrolidin-1-yl)pyrimidin-4-yl]-L-leucinamide

MS: APCI(+ve) 393(M+1)

Example 34
N~1~~-(Cyanomethyl)-N~2~~-(2-{methyl[(3-methylisoxazol-5-yl)methyl]amino} pyrimidin-4-yl)-L-leucinamide

MS: APCI(+ve) 372(M+1)

Measurement of Cathepsin S activity.

QFRET Technology (Quenched Fluorescent Resonance Energy Transfer) was used to measure the inhibition by test compounds of Cathepsin S-mediated cleavage of the synthetic peptide Z-Val-Val-Arg-AMC. Compounds were screened at five concentrations in duplicate and the pIC_{50} values reported.

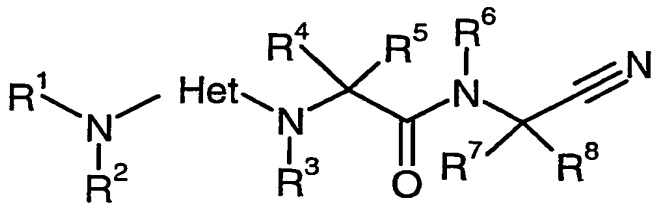
Synthetic substrate, 20□M [final]Z-Val-Val-Arg-AMC in phosphate buffer were added to a 96 well black Optiplate. The assay plates were pre-read for compound auto fluorescence on SpectraMax Gemini at 355nM excitation and 460nM emission. 250pM [final] rHuman Cathepsin S in phosphate buffer was added and incubated for 2h at room temperature on the SpectraMax Gemini, taking readings every 20min at 355nM excitation and 460nM emission.

Activity Based template (5PTB-8) used the auto fluorescent corrected data to calculate the percentage inhibition for each compound concentration using the relevent plate controls. This data was used to construct inhibition curves and pIC_{50} estimated by non-linear regression using a 4 parameter logistic model.

5

CLAIMS

1. A compound of formula (I):



(I)

R^1 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^2 is independently aryl, heteroaryl or a group C_{1-6}alkylR^9, $CO(C_{1-6}alkyl)R^9$ or $SO_2(C_{1-6}alkyl)R^9$;

or R^1 and R^2 together with the nitrogen atom to which they are attached form a 4 to 7-membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by one or more C_{1-6} alkyl, amino, hydroxy, CO_2C_{1-6} alkyl, COC_{1-6} alkyl, halogen, C_{1-6} alkylhydroxy, $NR^{10}R^{11}$ where R^{10} and R^{11} are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR^1 group, C_{1-6} alkyl$NR^{12}R^{13}$ where R^{12} and R^{13} are independently hydrogen or C_{1-6} alkyl, $CONR^{12}R^{13}$, or optionally substituted by C_{1-6}alkylR^9, aryl, phenoxy, COaryl, COheteroaryl or a heteroaryl group, the latter six groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, $CONR^{12}R^{13}$, $SO_2NR^{12}R^{13}$, SO_2R^{12}, trifluoromethyl, $NHSO_2R^{12}$, $NHCOR^{12}$, ethylenedioxy, methylenedioxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkyl $NR^{10}R^{11}$, SR^{12} or $NR^{10}R^{11}$;

Het is a heteroaryl ring chosen from pyridine, pyrimidine, pyrazine, pyridazine or triazine and optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, $CONR^{12}R^{13}$, $SO_2NR^{12}R^{13}$, SO_2R^{12}, trifluoromethyl, $NHSO_2R^{12}$, $NHCOR^{12}$, C_{1-6} alkyl, C_{1-6} alkoxy, SR^{12} or $NR^{10}R^{11}$;

R^3 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^4 is independently hydrogen, C_{1-8} alkyl, C_{3-8} cycloalkyl, arylC_{1-5}alkyl or heteroarylC_{1-5}alkyl, the latter three groups being optionally substituted by one or more halogen, amino, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, SR^{12} or $NR^{10}R^{11}$;

R^5 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^6 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^7 is independently hydrogen, C_{1-6} alkyl or C_{3-6} cycloalkyl;

R^8 is independently hydrogen, aryl, heteroaryl or C_{1-6} alkyl optionally substituted with one or more aryl, heteroaryl, halogen, amino, hydroxy, carboxy, $CONR^{12}R^{13}$, $SO_2NR^{12}R^{13}$, SO_2R^{12}, $NHSO_2R^{12}$, $NHCOR^{12}$, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, SR^{12} or $NR^{10}R^{11}$;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which R^1 is hydrogen or C_{1-6}alkyl and R^2 is CH_2R^9 or $CH_2CH_2R^9$ where R^9 is phenyl or a 5- or 6-membered aromatic ring containing one or two heteroatoms and optionally substituted by C_{1-6}alkyl

3. A compound according to claim 1 or 2 in which R^1 and R^2 form a piperidine, piperazine, pyrrolidine, morpholine, or thiomorpholine ring optionally substituted by CH_2OH, CH_2CH_2OH, hydroxy, $CONH_2$, phenyl, phenoxy, C(O)-furyl, the latter three groups being optionally substituted by halogen, in particular chloro

4. A compound according to any one of claims 1 to 3 in which R^3 is hydrogen.

5. A compound according to any one of claims 1 to 4 in which R^4 is hydrogen.

6. A compound according to any one of claims 1 to 5 in which R^5 is hydrogen or phenyl optionally substituted by C_{1-6} alkyl or C_{1-6} alkoxy.

7. A compound of formula (I) selected from:

N~1~-[Cyano(2-methoxyphenyl)methyl]-N~2~-(2-morpholin-4-ylpyrimidin-4-yl)-L-leucinamide

N~1~-[Cyano(2-methoxyphenyl)methyl]-N~2~-(2-piperazin-1-ylpyrimidin-4-yl)-L-leucinamide,

N-[Cyano(2-methoxyphenyl)methyl]-N-(2-morpholin-4-ylpyrimidin-4-yl)-L-phenylalaninamide

N~1~-[Cyano(2-methoxyphenyl)methyl]-3-cyclohexyl-N~2~-(2-morpholin-4-ylpyrimidin-4-yl)-L-alaninamide

N-[2-(Benzylamino)pyrimidin-4-yl]-N-(cyanomethyl)-L-phenylalaninamide

N-{2-[Benzyl(methyl)amino]pyrimidin-4-yl}-N-(cyanomethyl)-L-phenylalaninamide

N-{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N-(cyanomethyl)-L-phenylalaninamide

N~2~-[2-(Benzylamino)pyrimidin-4-yl]-N~1~-(cyanomethyl)-3-cyclohexyl-L-alaninamide

N~2~-{2-[Benzyl(methyl)amino]pyrimidin-4-yl}-N~1~-(cyanomethyl)-3-cyclohexyl-L-alaninamide

N~2~-{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-3-cyclohexyl-L-alaninamide

N~1~-(Cyanomethyl)-N~2~-(4-morpholin-4-ylpyrimidin-2-yl)-L-leucinamide

N~1~-(Cyanomethyl)-N~2~-(2-morpholin-4-ylpyrimidin-4-yl)-L-leucinamide

N~1~-(Cyanomethyl)-N~2~-[2-(4-hydroxy-4-phenylpiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide

N~1~-(Cyanomethyl)-N~2~-{2-[methyl(pyridin-3-ylmethyl)amino]pyrimidin-4-yl}-L-leucinamide

N~2~-{2-[Benzyl(methyl)amino]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide

N~2~-{2-[4-(4-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide,

N~2~-{2-[4-(5-Chloropyridin-2-yl)piperazin-1-yl]pyrimidin-4-yl}-N~1~-(cyanomethyl)-L-leucinamide,

N~1~-(Cyanomethyl)-N~2~-{2-[methyl(thien-3-ylmethyl)amino]pyrimidin-4-yl}-L-leucinamide

N~1~-(Cyanomethyl)-N~2~-(2-thiomorpholin-4-ylpyrimidin-4-yl)-L-leucinamide

N~1~-(Cyanomethyl)-N~2~-[2-(4-phenylpiperazin-1-yl)pyrimidin-4-yl]-L-leucinamide

N~1~-(Cyanomethyl)-N~2~-{2-[2-(hydroxymethyl)piperidin-1-yl]pyrimidin-4-yl}-L-leucinamide

N~1~~(Cyanomethyl)-N~2~~{2-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]pyrimidin-4-yl}-L-leucinamide
N~1~~(Cyanomethyl)-N~2~~[2-(4-hydroxypiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide
N~1~~(Cyanomethyl)-N~2~~{2-[4-(2-furoyl)piperazin-1-yl]pyrimidin-4-yl}-L-
N~2~~{2-[3-(Aminocarbonyl)piperidin-1-yl]pyrimidin-4-yl}-N~1~~(cyanomethyl)-L-leucinamide
N~1~~(Cyanomethyl)-N~2~~{2-[methyl(2-pyridin-2-ylethyl)amino]pyrimidin-4-yl}-L-leucinamide
N~2~~[2-(4-Benzylpiperidin-1-yl)pyrimidin-4-yl]-N~1~~(cyanomethyl)-L-leucinamide
N~1~~(Cyanomethyl)-N~2~~[2-(4-pyridin-2-ylpiperazin-1-yl)pyrimidin-4-yl]-L-leucinamide
N~1~~(Cyanomethyl)-N~2~~[2-(4-phenylpiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide
N~1~~(Cyanomethyl)-N~2~~{2-[4-(2-hydroxyethyl)piperidin-1-yl]pyrimidin-4-yl}-L-leucinamide
N~2~~{2-[4-(3-Chlorophenyl)piperazin-1-yl]pyrimidin-4-yl}-N~1~~(cyanomethyl)-L-leucinamide
N~1~~(Cyanomethyl)-N~2~~[2-(4-phenoxypiperidin-1-yl)pyrimidin-4-yl]-L-leucinamide
N~1~~(Cyanomethyl)-N~2~~[2-(3-phenylpyrrolidin-1-yl)pyrimidin-4-yl]-L-leucinamide
N~1~~(Cyanomethyl)-N~2~~(2-{methyl[(3-methylisoxazol-5-yl)methyl]amino}pyrimidin-4-yl)-L-leucinamide
and pharmaceutically acceptable salts thereof.

8. A compound of formula (I) as defined in any one of claims 1 to 7 for use in therapy.

9. A pharmaceutical composition which comprises a compound of the formula (I) as defined in any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

10. A method for producing inhibition of a cysteine protease in a mammal, such as man, in need of such treatment, which comprises administering to said mammal an effective amount of a compound of the present invention as defined in any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof.

11. A method for treating pain, such as neuropathic pain, in a mammal, such as man, in need of such treatment, which comprises administering to said mammal an effective amount of a compound as defined in any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001931

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 239/42, C07D 401/04, C07D 413/04, A61K 31/506, A61P 19/10
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0168645 A2 (AXYS PHARMACEUTICALS, INC.), 20 Sept 2001 (20.09.2001), see the claims --	1-11
X	WO 02069901 A2 (MERCK FROSST CANADA & CO.), 12 Sept 2002 (12.09.2002), see the claims -- --------	1-11

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 February 2004	25 -02- 2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer CARLOLINA GÓMEZ LAGERLÖF/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT
Information on patent family members

24/12/2003

International application No.
PCT/SE 2003/001931

WO	0168645	A2	20/09/2001	AU	4576401	A	24/09/2001
WO	02069901	A2	12/09/2002	CA	2439415	A	12/09/2002
				EP	1372655	A	02/01/2004

INTERNATIONAL SEARCH REPORT

International application No.
PCT SE 2003/001931

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10-11
because they relate to subject matter not required to be searched by this Authority, namely:
see extra sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT SE 2003/001931

Box II.1

Claims 10-11 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.